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Dated 17 April 2000

05APR00 E526906-1 D01030
P01/7700 0.00-0008179.4

Patents Form 1/77

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1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

05 APR 2000

1.	Your Reference	MA/PG3974
2.	Patent application number *(The Patent office will fill in this part)*	0008179.4
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 0NN GB
	Patents ADP number *(if you know it)*	4735870003
	If the applicant is a corporate body, give the country/state of its corporation	GB
4	Title of the invention	CHEMICAL PROCESS
5	Name of your agent *(if you know one)*	MICHAEL ATKINSON (SEE CONTINUATION SHEET)
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXO WELLCOME PLC GLAXO WELLCOME HOUSE, BERKELEY AVENUE GREENFORD, MIDDLESEX UB6 ONN, GB
	Patents ADP number *(if you know it)*	6990527001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
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YES

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Continuation sheets of this form	1
Description	6
Claim(s)	2
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature MICHAEL AKTINSON Date 4 APRIL 2000

AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

Kim Allen

020-8966 5721

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Patents Form 1/77

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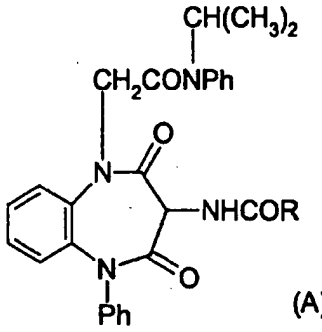
CHEMICAL PROCESS

The present invention relates to an improved process for preparing an intermediate for use in the synthesis of Cholecystokinin (CCK) agonists.

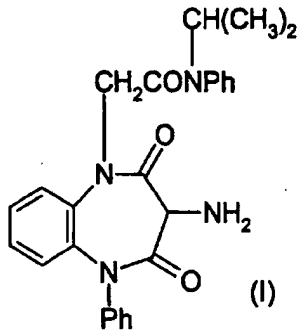
WO94/24149 describes a class of 1,5-benzodiazepine derivatives having an agonist action at the CCK-A receptor.

A particular interesting group of 1,5-benzodiazepine derivatives described therein may be represented by the general formula (A)



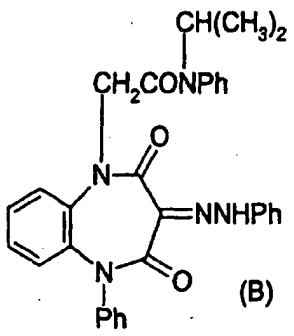
(A)

The compounds of formula A are conveniently prepared from the 3-amino derivative (I).



(I)

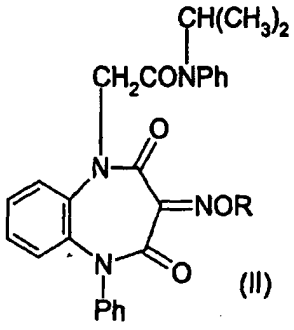
WO94/24149 teaches that such 3-amino-1,5- benzodiazepine derivatives may be prepared by reduction of the corresponding phenylhydrazone and the preparation of the compound of formula (I) by the reduction of the corresponding phenylhydrazone (B), is specifically described in intermediate (II) therein



(B)

Reduction of the hydrazone (B) to give the amine (I) also results in the formation of aniline. This is a highly toxic product, the generation of which should be avoided if at all possible in a commercial process and thus there is a need to find an alternative synthesis to the primary amine (I) which avoids the generation of aniline and provides the required product in good yield.

We have now found that the required amine (I) can be prepared in high yield and without the generation of toxic side products by concomitant reduction and hydrogenolysis of the corresponding oxime (II), wherein R is an optionally substituted benzyl group.



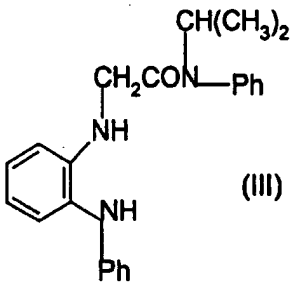
(II)

Thus the present invention provides for a process for preparing the amine (I) by concomitant reduction and hydrogenolysis of the oxime (II) followed, if desired, by isolation of the compound as an acid addition salt thereof.

The concomitant reduction and hydrogenolysis is conveniently carried out using a Palladium catalyst e.g. Palladium on charcoal catalyst in the presence of hydrogen or ammonium formate in a solvent such as an alkanol e.g. ethanol, isopropanol or an aqueous ethanol, e.g. aqueous ethanol, or tetrahydrofuran

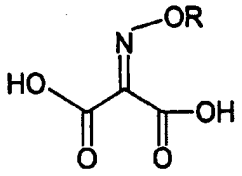
For the reaction the group R is conveniently benzyl or a substituted benzyl group e.g. p-methoxybenzyl or benzhydryl.

The oxime (II) may conveniently be prepared by reaction of the ortho-phenylene diamine derivative (III)



(III)

with an activated derivative of the di-acid (IV), wherein R is an optionally substituted benzyl group.



(IV)

Conveniently, the activated derivative of the di acid (IV) is the corresponding diacylhalide e.g. chloride and this is prepared in situ by reaction of the di-acid (IV) with an oxalyl halide e.g. oxalyl chloride. The reaction is conveniently carried out in an aprotic solvent such as an ester e.g. ethyl acetate, dichloromethane, toluene, or dimethoxyether or mixtures thereof, and in the presence of dimethylformamide.

The di acid (IV) is conveniently prepared by reaction of a dialkyl ketomalonate e.g. diethyl ketomalonate with the coresponding hydroxylamine derivative $RONH_2$ in a solvent such as an alkanol or industrial methylated spirits and in the presence of a base e.g. pyridine, followed by reaction with aqueous sodium hydroxide.

The following examples, which are non-limiting, illustrate the invention.

In the Examples the abbreviations EtOAc = ethyl acetate; MeOH = methanol, DMF = N, N-dimethylformamide; IPA = isopropyl alcohol; IMS = industrial methylated spirits.

Intermediate 1

Diethyl 2-[(benzyloxy)imino]malonate

Di-ethylketomalonate (60g) was added at 20°C to a stirred suspension of O-benzylhydroxylamine (57.8g) in IMS (500ml) containing pyridine (30ml). The reaction was heated at 75°C for 4hr. The reaction was cooled and solvents removed under reduced pressure. The residue was partitioned between EtOAc (500ml) and water (300ml) and the organic layer separated, washed with water (250ml) and dried over $MgSO_4$. Solvents were evaporated to give the title compound 95.3g, as a colourless oil (99%th, ca 3%w/w residual EtOAc) which was used without further purification.

1H NMR (300MHz, $CDCl_3$) 7.4 (m, 5H), 5.35 (s, 2H), 4.35 (m, 4H), 1.3 (m, 6H).

Intermediate 2

2-[(benzyloxy)imino]malonic acid

To a solution of Intermediate 1 (40g) in MeOH (80ml) was added 2M NaOH (200ml) over 20 mins. The reaction was stirred at room temperature for 2hr. MeOH was removed under reduced pressure and the residual solution was acidified to pH 2 by dropwise addition of conc.HCl (~30ml) while cooling to

maintain the temperature below 35°C. A thick white slurry was formed which was diluted with water (50ml) to aid mobility. The solids were collected by filtration, washed with chilled water (25ml) and dried in vacuo at 55°C to give the title compound as a white solid (17g) found to contain ca.10%w/w residual inorganic salts. Corrected yield ~ 45%th. Used without further purification.

1H NMR (300MHz, D_2O) 7.4 (m, 5H), 5.2 (s, 2H)

Intermediate 3

2-[-3-[(Benzyloxy)imino]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepinyl)-N-isopropyl-N-phenylacetamide

Oxalyl chloride (38.3g) was added dropwise (~1hr) to a stirred suspension of Intermediate 2 (40g, corrected for salt content to 31.4g) in EtOAc (200ml) containing DMF (0.5ml, 5 mol%). The mixture was stirred at 25°C for 0.5 hour then filtered through a pad of Dicalite, washing with EtOAc (40ml) to give a clear yellow solution. The solution was added (~5mins) to a stirred slurry of N-isopropyl-N-phenyl-2-(2-phenylaminophenylamino)-acetamide (50g) in EtOAc (120ml) at 25°C. The mixture was warmed to 60°C and a dark purple solution formed. After 1hr, EtOAc (200ml) was removed by atmospheric distillation. IPA (120ml) and water (40ml) were added and the mixture distilled further to remove more solvent (80ml). IPA (40ml) and water (40ml) were added and a further amount of solvent was distilled out (80ml). The reaction mixture was cooled to 25 °C over 1.5hr and the solids collected by filtration. The solids were washed with IPA (2 x 120 ml), water (1 x 120ml) and finally IPA again (1 x 40ml) then dried in vacuo at 55°C to give the title compound as a salmon pink powder (56.6g).

1H NMR (300MHz, $CDCl_3$) 2:1 mixture of isomers about the oxime 7.6-6.95 (m. 18H), 6.9 (t 1H), 5.3 (m, 2H), 4.95 (m, H), 4.65 (d, 0.33H), 4.4 (d, 0.67H), 4.1 (d, 0.67H), 4.0 (d, 0.33H), 0.95 (m, 6H)

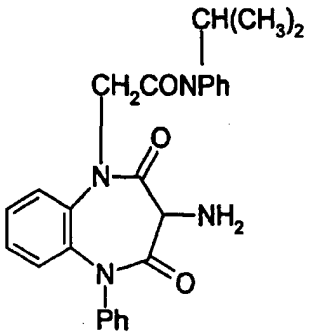
Example 1

(±)-2-(3-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo-[b][1,4]diazepen-1-yl)-N-isopropyl-N-phenylacetamide

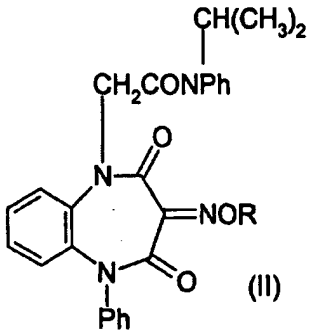
To a stirred suspension of Intermediate 3 (3g) and ammonium formate (2.08g) in IMS (30ml) and water (3ml) was added 5% Pd/C (50% w/w water) (0.25g). The mixture was heated under a nitrogen atmosphere at 60°C overnight. The hot reaction mixture was filtered through Dicalite to remove the catalyst. The catalyst was washed with hot IMS (60ml) and filtered. The filtrates were concentrated under reduced pressure to give the title compound as a white solid (2.34g).

Claims

1. A process for the preparation of the compound of formula (I)



or an acid addition salt thereof which comprises reacting a compound of formula (II)

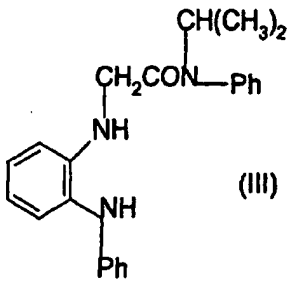


(II)

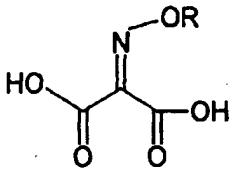
wherein R is an optionally substituted benzyl group under reductive hydrogenolysis conditions, followed, if required, by isolation of the compound as an acid addition salt thereof.

2. A process as claimed in claim 1 wherein the reductive hydrogenolysis is carried out using a palladium catalyst.

3. A process as claimed in claim 1 or claim 2 wherein the compound of formula (II) has been prepared by reaction of the ortho phenylene diamine derivative (III) with an activated derivative of the di-acid (IV),



(III)



(IV)

wherein R is an optionally substituted benzyl group.

4. A process as claimed in claim 3 wherein the activated derivative of the di-acid (IV) is the di-acylchloride.

5. A process as claimed in any of claims 1 to 4 wherein R is benzyl.